Available online on 22.02.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Comparison of the Effectiveness of Single Oral Antidiabetic Drugs with Combination Antidiabetic Drugs in Lowering Blood Sugar in Type 2 Diabetes Mellitus Patients at UKI General Hospital in 2014-2017

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Article Info:

Article History:

Received 31 December 2021
Reviewed 06 February 2022
Accepted 11 February 2022
Published 22 February 2022

Cite this article as:

Lumbantobing R, Kurniyanto, Comparison of the Effectiveness of Single Oral Antidiabetic Drugs with Combination Antidiabetic Drugs in Lowering Blood Sugar in Type 2 Diabetes Mellitus Patients at UKI General Hospital in 2014-2017, Journal of Drug Delivery and Therapeutics. 2022; 12(1-s):118-122

DOI: http://dx.doi.org/10.22270/jddt.v12i1-s.5219

Abstract

Diabetes Mellitus is a disease characterized by hyperglycemia or the glucose in the blood increased or beyond ordinary. The national prevalence of Diabetes Mellitus in Indonesia is 6,9%. Patients with Diabetes Mellitus can be given antidiabetic drugs such as sulfonylurea and glinid. The antidiabetic drug can be consumed as a combination or single. This study aims to determine whether there is a significant efficacy comparison between antidiabetic combination therapy and single antidiabetic therapy. This study is a retrospective casual research by looking at the medical record. From 30 patients, 15 patients using oral antidiabetic combination therapy and 15 patients using oral antidiabetic single therapy, there were mean differences on the first day where patients using oral antidiabetic single therapy mean 228,47 and patients using oral antidiabetic combination therapy mean 294,07. There is no significant difference between single antidiabetic therapy or antidiabetic combination therapy from the statistic test.

Keywords: Diabetes, Antidiabetic effectiveness

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INTRODUCTION

Diabetes mellitus (DM) is a disease characterized by hyperglycemia or a condition in which glucose in the blood increases or exceeds normal limits, which occurs due to the pancreas's deficiency or decreased effectiveness of insulin. According to the International Diabetes Federation (IDF), in 2015, the incidence of diabetes mellitus in the world was 415 million people, where the proportion of the incidence of type 2 diabetes mellitus was 95% of the world's population suffering from diabetes. It was also stated that Indonesia was ranked seventh globally, with an estimated number of people with DM as many as 10 million people. It is estimated that by 2040, the number will increase to 16.2 million. DM is ranked fourth in chronic disease in Indonesia based on its prevalence. Riskesdas data in 2013 stated that the national prevalence of DM was 6.9%. Referring to the national prevalence, DKI Jakarta has a total prevalence of DM of as much as 2.5%, where DKI Jakarta is ranked 2nd out of 33 provinces in Indonesia. Many sufferers are in the age range of 56-64 years, with a prevalence of 4.8% [1]. The increasing prevalence of DM requires the Indonesian government always to handle and treat DM patients.

According to Perkeni (Indonesian Endocrinology Association), handling cases of type 2 DM consists of 4 pillars, namely: (1) education; (2) meal planning (diabetic diet); (3) physical exercise or exercise; and (4) pharmacological intervention which may consist of administering oral antidiabetic drugs (OAD) alone or in combination and administration of insulin. Pharmacological intervention is given if blood glucose has not decreased only by changing lifestyle [2; 3]. Patients with type 2 diabetes can be given OAD drugs such as Sulfonylureas, Glinids, Biguanides, Thiazolidinediones (TZD), and alpha-glucosidase inhibitors DPP-IV and SGLT-2. Administration can be done singly or in combination early on by looking at the patient's clinical condition and starting with a low dose.

The effectiveness of OAD drugs given alone and in combination to patients for lowering blood glucose is not yet known clearly because they often differ depending on the patient's condition. Based on this description, it is necessary to compare the effectiveness of oral antidiabetic drugs. Therefore, researchers are encouraged to conduct this study to compare the effectiveness of a single oral antidiabetic drug with a combination in patients with diabetes mellitus at the Indonesian Christian University General Hospital from January 2014 to July 2017. Combined oral antidiabetic drugs are more effective than single oral antidiabetic drugs in lowering blood sugar in type 2 diabetes mellitus?.

LITERATURE REVIEW

Diabetes mellitus (DM) is a group of glucose metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, insulin action or both [4]. This chronic metabolic disease is caused by the pancreas not producing enough insulin or the body not using the insulin it produces effectively. Insulin is a hormone that regulates the balance of blood sugar levels, increasing the concentration of glucose in the blood (hyperglycemia). Type 1 diabetes mellitus, also known as IDDM, is a glucose metabolic disease caused by damage to the beta cells of the islets of Langerhans in the pancreas. The damage that occurs can be caused by an autoimmune reaction that destroys the islets of Langerhans beta cells so that the amount of insulin produced is reduced or even stopped. Apart from autoimmunity, some causes of IDDM have no known aetiology (idiopathic) [5].

Type 2 diabetes mellitus is a metabolic disease characterized by hyperglycemia due to the insensitivity of cells to insulin due to impaired insulin function (insulin resistance) and decreased insulin secretion. Type 2 diabetes mellitus is also referred to as non-insulin-dependent diabetes mellitus (NIDDM) because the beta Langerhans cells of the pancreas still produce insulin even though they have decreased [6]. Several factors are known to influence the occurrence of diabetes type 2, among others, due to genetic disorders, age, lifestyle and wrong diet,

The diagnosis of DM is based on the examination of blood glucose levels. The recommended glucose test is an enzymatic glucose test with venous blood plasma. Blood glucose used for assessment is fasting blood glucose, postprandial and HbA1c [7].

Table 1: Value of Blood Sugar Examination

	Fasting blood glucose	Post-prandial blood glucose	HbA1c
Diabetes	≥ 126 mg/dL	≥ 200 mg/dL	≥ 6.5%
Normal	<100 mg/ dL	< 140 mg/dL	< 5.7%

Non-Pharmacological Therapy for Type 2 Diabetes Mellitus - Good nutrition or diet is the key to successful diabetes management. The recommended diet is food with a balanced composition of carbohydrates, proteins and fats. The goals of dietary treatment in diabetes are [8]: a) Achieve and then maintain near normal blood glucose levels; b) Achieve and maintain near-optimal lipid levels; c) Prevent complications, and d) Improving the quality of life. Nutrition therapy is recommended for all patients with diabetes mellitus; the most important of all nutritional therapy is optimal metabolic results and prevention of complications.

In addition, exercising can lower and maintain normal blood sugar levels. With the principle that there is no need for heavy exercise, a light exercise done regularly will ideally affect health. Some examples of recommended sports include walking or jogging, cycling, swimming, etc. Exercise will increase the use of glucose so that glucose levels in the body fall and remain normal.

Pharmacological Therapy of Type 2 Diabetes Mellitus - The main goal in managing diabetes mellitus is to normalize or regulate insulin activity and blood glucose levels to reduce the occurrence of complications. Drugs used to treat diabetes are usually in the form of oral drugs other than insulin injection. Its use is adapted to the clinical situation of diabetic patients [9].

There is a possibility of Primary failure, and Secondary failure in the therapy carried out. Primary failure is a condition where the dose (starting from the lowest) given is considered ineffective so that the dose is started to be increased until it reaches the effective dose for the patient. If it remains ineffective until the highest or maximum administration dose, then secondary failure occurs in the patient. Secondary failure is a condition where failure occurs with the highest dose of therapy, so it is necessary to change the drugs used and even combine drugs. Combinations of drugs are also performed on complications.

Sulfonylureas-Drugs of this class have the main effect of stimulating insulin secretion by the beta cells of Langerhans in the pancreas. This drug is no longer helpful in people with diabetes with Langerhans beta-cell damage. Weight gain and hypoglycemia are the main side effects of sulfonylurea stimulation of Langerhans beta cells [10]. The pharmacodynamics of sulfonylureas begins with binding and blocking ATP sensitive potassium ion (K+) channels. This reduced K+ condition causes membrane depolarization so that calcium ion (Ca+) channels open and Ca+ enters from the outside and releases insulin. The intestine absorbs sulfonylurea derivatives well. After absorption, the drug is dispersed throughout the extracellular fluid. Some sulfonylureas are bound to plasma proteins in plasma, mainly albumin (70%-90%). Pharmacokinetics that occur are different in each sulfonylurea preparation [11].

Table 2: Pharmacokinetics of the Sulfonylureas

	Description
Tolbutamide	The intestines rapidly absorb it, reaching maximal levels in 3-5 hours. The kidneys will carry out excretion.
Chlorpropamide	Well absorbed in the intestine, half-life 24-48 hours, metabolized and rapidly excreted through the kidneys.
Glipizide	Well, it is absorbed by the intestines. The half-life of this drug is about 3-4 hours. Metabolism occurs in the liver, and 10% is excreted intact through the kidneys.
Glibenclamide	It has a half-life of ±4 hours metabolized in the liver; 25% is excreted in the urine and the bile.

Glinid-This class of drugs has the same action as the sulfonylureas, which stimulates Langerhans beta cells in the pancreas to secrete insulin. This group stimulates insulin by closing ATP-independent K channels in pancreatic beta cells. Repaglinide and nateglinide are 2 types of glinide drugs. With oral administration, absorption is rapid, and peak levels are reached within 1 hour. Its half-life is 1 hour, so it should be given several times a day, before meals. The central metabolism occurs in the liver, and the metabolites are inactive. About 10% is metabolized in the kidneys. Patients with impaired liver or kidney function should be given with caution. The main side effects are hypoglycemia and gastrointestinal disturbances [12].

Biguanides-This group of Biguanides has the effect of lowering blood glucose levels in people with diabetes and increasing the sensitivity of cells to insulin. This decrease in blood glucose levels is caused by an increase in glucose intake into muscles, a decrease in increased gluconeogenesis and an inhibition of glucose absorption in tissues. Metformin is the only biguanide available. Metformin is the drug of the first choice in overweight patients in whom a strict diet fails to control diabetes [13]. Metformin reaches peak blood levels after 2 hours and is excreted in the urine intact with a half-life of 2-5 hours. Metformin is eliminated by renal tubular secretion and glomerular filtration. This drug does not cause hypoglycemia in non-diabetic patients unless excessive doses are given, and the metformin can cause lactic acidosis in patients with impaired renal function. Therefore, it should not be given even to patients with mild renal impairment.

Thiazolidinediones (rosiglitazone and pioglitazone) bind to peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor in muscle and fat cells. This group has the effect of reducing insulin resistance by increasing the amount of glucose transporting protein, thereby increasing peripheral glucose uptake. Drugs belonging to this group are Pioglitazone [14]. Thiazolidinediones are contraindicated in patients with heart failure because they can exacerbate oedema/fluid retention and impair liver function (periodic monitoring is necessary).

Alpha-glucosidase inhibitors- These drugs work competitively to inhibit the action of alpha-glucosidase enzymes in the digestive tract so that they can reduce postprandial hyperglycemia. Drugs belonging to this group are Acarbose and Miglitol. The onset of action of Acarbose is 0.5 hours, half-life 1-2 hours, duration 4 hours. The onset of action of Miglitol is 2-3 hours with a half-life of 3 hours. Alpha-glucosidase inhibitors have a mechanism of action by inhibiting the action of the alpha-glucosidase enzyme found on the "brush border" on the surface of the small intestine membrane. Alpha-glucosidase enzymes function as enzymes that break down carbohydrates into glucose in the small intestine. With the administration of alpha-glucosidase inhibitors, the hydrolyzed oligosaccharides will be reduced so that the breakdown and absorption of carbohydrates in the intestine will be reduced, and blood glucose levels will automatically decrease. Insulin levels are not affected because it acts on the intestines [15].

DPP-IV Inhibitors- This Dipeptidyl Peptidase-IV(DPP-IV) inhibitor class inhibits the action of the DPP-IV enzyme so that glucose-like peptide-1 (GLP-1) remains in high concentration and active form. GLP-1 is an enzyme that can powerfully stimulate the release of insulin and inhibit glucagon secretion. Drugs belonging to this group are Sitagliptin and Linagliptin [16].

SGLT-2 Inhibitors-SGLT 2 inhibitors work by lowering glucose by blocking glucose reabsorption in the proximal renal tubule. This medicine can reduce weight and blood pressure. Examples are Canagliflozin, Dapagliflozin, Empagliflozin. This drug increases glucosuria. Possible side effects are genitourinary infection, polyuria, hypotension, dizziness, elevated LDL-C and transient creatinine elevation [17].

Combination Oral Antidiabetic Drugs-Combination therapy with oral antidiabetic drugs is given in the event of secondary failure of these drugs. This combination therapy, either separately or fixed-dose combination, must use two drugs with different mechanisms of action. Diabetes mellitus is a disease that can cause various kinds of complications [18].

RESEARCH METHOD

This study is an ex post facto study looking at the average difference in blood sugar reduction in 2 groups of subjects. It is done to determine whether there is a significant comparison of effectiveness between a single oral antidiabetic drug and a combined oral antidiabetic drug in lowering blood sugar in diabetic patients—Mellitus type 2 who underwent hospitalization at UKI General Hospital for the period January 2014 – July 2017. The instrument used in this study was the medical record status of type 2 diabetes mellitus patients who had received antidiabetic treatment who underwent hospitalization at UKI Hospital for January 2014 – July 2017, stationery and laptop for compiling data. This research was conducted in the medical records section of the UKI General Hospital. Data collection was carried out in October 2017 - December 2017. The population in this study was all inpatients with type 2 diabetes mellitus at UKI Hospital from January 2014 - to July 2017. Sampling was carried out using the Gay constant (1976), which offers the minimum size acceptable based on the type of research is.

For this type of ex post facto research or comparative causal research, 15 subjects from each group are needed. A random sampling method was used in this study, namely 15 subjects using a single oral antidiabetic drug and 15 subjects using a combination oral antidiabetic drug. Before assessing the raw data, firstly, a re-examination of the correctness of the data obtained and removing data that did not meet the research inclusion criteria was carried out. Researchers coded the selected data from the selection process to facilitate the SPSS (Statistical Package for the Social Sciences) program analysis. Coding is numerical code (number) to data that consists of several categories. The researcher entered the data done in the coding process into the Microsoft Excel program in the form of a table. The data that has been inputted is rechecked to make sure the data is clean from errors and ready for analysis. Data were analyzed by taking secondary data using the ex post facto method or causal-comparative research using the random sampling method. The samples were taken must meet the inclusion and exclusion criteria that the researcher has set. Then perform data analysis to compare effectiveness by noting a decrease in blood sugar after being given a single or a combination oral antidiabetic drug. Furthermore, based on the data that has been obtained, then data analysis is carried out with SPSS (Statistical Package for the Social Sciences) using normality test and T-test.

RESULT AND DISCUSSION

This study is an ex post facto or retrospective comparative causal study by looking at the average difference in blood sugar reduction in 2 groups of subjects to determine whether there is a significant effectiveness comparison between a single oral antidiabetic drug and a combined oral antidiabetic drug in lowering blood sugar. The number of samples in this study was 30 patients, namely 15 patients using a single oral antidiabetic drug and 15 patients using a combined oral antidiabetic drug.

Table 3: Average (Mean) Blood Sugar Value Based on Drug Type

	Drug Type	Mean
Check Blood Sugar 1	Single	228,47
	Combination	294,07
Check Blood Sugar 2	Single	179,13
	Combination	221,07
Check Blood Sugar 3	Single	137,00
	Combination	169,80

The table above show that the average decrease in blood sugar from the first day to the third day appears to be decreasing. The table also shows that the average decrease in blood sugar ratio in patients taking a single antidiabetic drug was not significantly different from the average decrease in patients using a combination antidiabetic drug.

Table 4: Average Blood Sugar Value Regardless of Drug Type

	Mean
Check Blood Sugar 1	261,27
Check Blood Sugar 2	200,10
Check Blood Sugar 3	153,40

Table 4 shows a decrease in the average blood sugar value from the first day to the third day regardless of the drug used.

This test was conducted to determine whether there was a significant difference in reducing blood sugar in the use of 2 types of drugs. The T-Test will get the p-value (sig.) for each variable. It is stated that there is a significant difference when getting P < 0.050.

Table 5: Comparison of Significant Decreases between Drug Types

	Sig. (Antara Kedua Tipe Obat)
Check Blood Sugar 1	,024
Check Blood Sugar 2	,054
Check Blood Sugar 3	,089

The table above shows a significant reduction in the comparison between a single oral antidiabetic drug and a combination antidiabetic drug on the first day.

The tables and graphs in the Univariate analysis show that the average blood sugar value decreased from the first day to the third day. Graph 1 shows that the average decrease in blood sugar between a single antidiabetic and a combination antidiabetic is not proportional.

The table in the Bivariate analysis shows a significant difference between the use of oral antidiabetic drugs with a single on the first day of blood sugar checks. Most of the patients taking combination antidiabetic drugs have higher blood sugar than patients taking single antidiabetic drugs.

Many factors inhibit or interfere with the work of a drug, one of which is age. In patients who are elderly (elderly), physiological functions (such as organs) decrease so that the absorption process of the drug takes longer [19]. The patient's co-morbidities also affect the work of drug metabolism. The results of drug metabolism that can be maximally absorbed are reduced because there are disturbances in the organs in charge of absorbing them, such as the liver, kidneys and intestinal (intestines) organs. In addition, the work of antidiabetic drugs is not optimal; it can be caused by the use of other drugs whose effects reduce the effectiveness of antidiabetic drugs [20]. Hereditary or genetically acquired factors can also affect the action of a drug. Genetic makeup can influence drug biotransformation. This factor determines whether there are naturally occurring enzymes capable of breaking down drugs. There are interactions between drugs and other drugs that give more effect by supporting each other (synergistic reactions) and some that inhibit each other (antagonistic reactions) [21]. It is also one of the factors that can inhibit the effectiveness of a drug where a drug becomes ineffective due to the antagonistic nature of the other drug compounds consumed. Various factors that can inhibit the action of drugs become a consideration in drug administration to get excellent and maximum results.

CONCLUSION

Antidiabetic drugs can lower a patient's blood sugar, either used alone or in combination. The study results obtained by using medical record data from patients with type 2 diabetes mellitus who were hospitalized showed that there was no significant effectiveness comparison between single antidiabetic drugs and the combination used by the patients. Thus, to better adjust the use of antidiabetic drugs in terms of quantity, medication and duration of treatment with the patient's health condition. Increase education to patients to continue taking drugs and maintain a good lifestyle after being discharged from the hospital. In addition, it is necessary to improve data completeness, information writing and clarity in writing data in medical records so that researchers can easily read them and get complete data.

REFERENCES

[1] Qaribi, Mahanta, Dewi Elizadiani Suza, and Rosina Tarigan. "Effect Of Education In Preventing Diabetic Foot Ulcers To Compliance And Quality Of Life The Diabetic Patients." European Journal of Molecular & Clinical Medicine 2021; 8(3).

[2] van de Laar, Floris Alexander. "Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes." Vascular health and risk management 2008; 4(6):1189. https://doi.org/10.2147/VHRM.S3119

[3] Trento, Marina, P. Passera, M. Bajardi, M. Tomalino, G. Grassi, E. Borgo, C. Donnola, Franco Cavallo, Piervincenzo Bondonio, and Massimo Porta. "Lifestyle intervention by group care prevents deterioration of Type II diabetes: a 4-year randomized controlled clinical trial." Diabetologia 2002; 45(9):1231-1239. https://doi.org/10.1007/s00125-002-0904-8

[4] Ozougwu, J. C., K. C. Obimba, C. D. Belonwu, and C. B. Unakalamba. "The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus." Journal of physiology and pathophysiology 2013; 4(4):46-57. https://doi.org/10.5897/JPAP2013.0001

[5] Xu, Yunzhi, and Guangjie Chen. "Mast cell and autoimmune diseases." Mediators of inflammation 2015 (2015). https://doi.org/10.1155/2015/246126

[6] Höppener, Jo WM, and Cees JM Lips. "Role of islet amyloid in type 2 diabetes mellitus." The international journal of biochemistry & cell biology 2006; 38(5-6):726-736. https://doi.org/10.1016/j.biocel.2005.12.009

[7] Jiang, Jingjing, Lin Zhao, Liu Lin, Minghui Gui, Qiqige Aleteng, Bingjie Wu, Shanshan Wang, Baishen Pan, Yan Ling, and Xin Gao. "Postprandial blood glucose outweighs fasting blood glucose and HbA1c in screening coronary heart disease." Scientific reports 2017; 7(1):1-7. https://doi.org/10.1038/s41598-017-14152-y

[8] Wilson, D. C., D. Kalnins, C. Stewart, N. Hamilton, A. K. Hanna, P. R. Durie, E. Tullis, and P. B. Pencharz. "Challenges in the dietary treatment of cystic fibrosis related diabetes mellitus." Clinical Nutrition 2000; 19(2):87-93. https://doi.org/10.1054/clnu.1999.0081

[9] Inzucchi, Silvio E., Richard M. Bergenstal, John B. Buse, Michaela Diamant, Ele Ferrannini, Michael Nauck, Anne L. Peters, Apostolos Tsapas, Richard Wender, and David R. Matthews. "Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)." Diabetes Spectrum 2012; 25(3):154-171. https://doi.org/10.2337/diaspect.25.3.154

[10] Pfeiffer, Andreas FH. "Oral hypoglycemic agents: Sulfonylureas and meglitinides." In Type 2 Diabetes, pp. 111-120. CRC Press, 2016.

[11] McLeod, James F. "Clinical pharmacokinetics of nateglinide." Clinical pharmacokinetics 2004; 43(2):97-120. https://doi.org/10.2165/00003088-200443020-00003

[12] Lewis, ALAN B., MICHAEL D. Freed, MICHAEL A. Heymann, SHARON L. Roehl, and ROSEMARY CHEN Kensey. "Side effects of therapy with prostaglandin E1 in infants with critical congenital heart disease." Circulation 64, no. 5 (1981): 893-898. https://doi.org/10.1161/01.CIR.64.5.893

[13] Nichols, Gregory A., Charles M. Alexander, Cynthia J. Girman, Sachin J. Kamal-Bahl, and Jonathan B. Brown. "Treatment

escalation and rise in HbA1c following successful initial metformin therapy." Diabetes Care 2006; 29(3):504-509. https://doi.org/10.2337/diacare.29.03.06.dc05-1937

[14] Chang, Kai Lun, Hai Ning Pee, Shili Yang, and Paul C. Ho. "Influence of drug transporters and stereoselectivity on the brain penetration of pioglitazone as a potential medicine against Alzheimer's disease." Scientific reports 2015; 5(1):1-7. https://doi.org/10.1038/srep09000

[15] Dubé, Philip E., Catherine L. Forse, Jasmine Bahrami, and Patricia L. Brubaker. "The essential role of insulin-like growth factor-1 in the intestinal tropic effects of glucagon-like peptide-2 in mice." Gastroenterology 2006; 131(2):589-605. https://doi.org/10.1053/j.gastro.2006.05.055

[16] Anbarasan, V. "Comparison on Efficacy and Safety of Linagliptin Vs. Sitagliptin Among Type 2 Diabetic Patients." PhD diss., Ultra College of Pharmacy, Madurai, 2014.

[17] Rosenthal, Norm, Gary Meininger, Kirk Ways, David Polidori, Mehul Desai, Rong Qiu, Maria Alba et al. "Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus." Annals of the New York Academy of Sciences 2015; 1358(1):28-43. https://doi.org/10.1111/nyas.12852

[18] Tripathi, Brajendra Kumar, and Arvind Kumar Srivastava. "Diabetes mellitus: complications and therapeutics." Medical science monitor 2006; 12(7):RA130-RA147.

[19] Lehne, Richard A., Linda A. Moore, Leanna J. Crosby, and Diane Bronkema Hamilton. Pharmacology for nursing care. Saunders/Elsevier, 2010.

[20] Chaudhury, Arun, Chitharanjan Duvoor, Vijaya Sena Reddy Dendi, Shashank Kraleti, Aditya Chada, Rahul Ravilla, Asween Marco et al. "Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management." Frontiers in endocrinology 2017; 8:6. https://doi.org/10.3389/fendo.2017.00006

[21] Chou, Ting-Chao. "Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies." Pharmacological reviews 2006; 58(3) 621-681 https://doi.org/10.1124/pr.58.3.10